Insert the following new claims:

18 21. A GnRH antagonist according to claim 1 wherein Xaa_5 is 4Aph(L-Hor) and Xaa_6 is D-Aph(Q) or D-Amf(Q) with R being H or methyl.

a6

22. A GnRH antagonist according to claim 19 having the formula:
Ac-D-2Nal-(A)D-Phe-D-3Pal-Ser-4Aph(carbamoyl)-D-4Aph(carbamoyl)-Leu-Lys(Ipr)-Pro-Xaa_{10}.

REMARKS

Indication of the allowance of claim 20 and the willingness to allow the subject matter of claims 2-11 and 16 is acknowledged with appreciation. Amendments are made to claims 1, 13 and 19 to overcome the objections set forth in the Office Action from the standpoint of indefiniteness. More specifically, claim 13 has been amended to insert a reference to the fact that Q is defined as in claim 1 upon which claim 13 is dependent. Thus, it is believed that the rejections under 35 U.S.C. §112 have been cured and should now be withdrawn.

Claim 1 has also been amended so as to limit Q_1 in the definition of Xaa_5 to either D- or L-Hor or D- or L-Imz. It is thus believed that claim 1, and dependent claims 2-11, 13-18 and new claim 21 should now be allowable because the prior art cited is clearly deficient in this recitation, as generally already acknowledged by the Examiner in her allowance of independent claim 20. New claim 21 is supported by Examples 1, 1A and 4.

Claims 2, 9-11, 14 and 16 have been amended so as to further clarify what is being claimed with respect to the isomers of hydroorotic acid. Claim 13 was also amended to correct the spelling of Pn so that it is consistent with the definition given on page 10, line 15; such a correction is also made to page 13, line 19. Moreover, page 10, line 15 and page 43, line 31, have been amended to remove any

reference to i-propionyl as it has come to the attention of the undersigned that the compound does not exist. Other clerical errors are also corrected throughout the specification which are believed to be evident upon their face. The change on page 12, line 25, supplies the correct name, as can be seen from U.S. Patent No. 5,565,574. In addition, a minor change is made to page 24, line 12, as it now appears that all of the t-butyl moiety may not be removed along with the removal of the Boc protecting group; the remainder would of course be removed at the time of cleavage from the resin when the other remaining protecting groups are removed. Claims 17 and 18 are amended so as to more particularly point out and distinctly define the subject matter being claimed. New claim 22 finds support in Example 1L.

Claim 19 has been amended to restrict Q to carbamoyl or methylcarbamoyl, as a result of which amendment this claim now recites GnRH antagonist peptides where the 5- and 6-position residues are either 4Aph or 4Amf, the side chains of which are modified with carbamoyl, methylcarbamoyl, Hor, or Imz. Claim 19 has also been amended to specify that these GnRH antagonists exhibit long duration of suppression of LH, which finds support at page 9, lines 15-16 and at page 26, lines 1-22. It is submitted that claim 19 defines subject matter that would not be obvious from the teachings in U.S. Patent No. 5,506,207 to Rivier et al. in view of the disclosure of U.S. Patent No. 5,296,468 to Hoeger et al. and the disclosure of Jiang et al. abstract. For the Examiner's convenience, a copy of the article from which the Jiang et al. abstract was prepared is being attached to this paper as Exhibit A.

As the Examiner recognizes, although the Rivier patent discloses a number of GnRH antagonists including that referred to herein as Acyline, as set forth on page 6, lines 7-12 of the specification, it does <u>not</u> teach the 5- and 6-position moieties being an aminophenylalanine or aminomethylphenylalanine residue the side chain of which is

modified with carbamoyl, methylcarbamoyl, Hor or Imz. The Examiner asserts that the disclosure of Hoeger et al. would alleviate this deficiency; however, it is submitted that this is simply not the case.

Although the Hoeger et al. patent contains some broad disclosure as to what modifications may be made in certain amino acid residue side chains, it truly contains only a single disclosure which is at all relevant to claim 19; this is found in Example XIV in columns 25 and 26 of the patent. That example discloses a GnRH antagonist wherein unsubstituted tyrosine appears in the 5-position and a residue having a linear side chain, namely D-lysine, is located in the 6-position, the terminal side chain amino group of which is modified by reaction with naphthyl isocyanate. By comparison with claim 19 as presently written, instead of disclosing a GnRH antagonist having the 6-position in the chain occupied by a phenylalanine moiety having its side chain modified by reaction with a linear isocyanate (and with a similar residue in the 5-position), Hoeger et al. merely discloses one GnRH antagonist wherein the 5-position contains the native residue of GnRH and wherein the 6-position residue is a Lys moiety modified with an aromatic (naphthyl) isocyanate.

The additional secondary reference to Jiang et al. contains no disclosure to cure this deficiency. As is apparent from the full Jiang et al. article, the disclosure with regard to the employment of 4Amf is based upon the synthesis of Peptide No. 4, with the observation being that these substitutions resulted in "a significant lowering of potency in the AOA (antiovulatory assay)". Thus, other than broadly disclosing the potential use of 4Amf, the Jiang et al. article really adds nothing to the disclosure of Hoeger et al.

It is submitted that there is nothing in the primary reference to Rivier et al. or the secondary reference to Hoeger et al. that would fairly suggest the synthesis of the GnRH antagonists now defined by amended claim 19

wherein the residues in the 5- and 6-positions are defined as set forth in the paragraph above. It is submitted that it is only in hindsight that one might select an obscure disclosure from the Hoeger et al. patent, which shows modifying a single amino acid residue with an aromatic isocyanate, and combine that disclosure with the teaching of the Rivier et al. patent so as to modify two adjacent residues, while at the same time choosing a nonaromatic isocyanate.

It is settled law that the combination of one reference with another is not proper unless there is some suggestion or motivation to make such a modification -- which cannot be only in the hindsight of Applicants' disclosure. In this respect, the decision of the CAFC in the case of *In re Fritch*, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) is particularly pertinent:

> "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hosp. Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purported obvious 'modification' of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification."

In an earlier decision in the case of *In re Fine*, 5 USPQ2d 1596, 1600 (Fed.Cir. 1988), the Court stated:

> ". . . One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

It is submitted that there is simply no suggestion of the desirability of the modification which the Examiner proposes to make.

In 1997, the Federal Circuit reiterated its *Fritch* decision holding of some five years earlier, stating:

> "A determination of obviousness must involve more than indiscriminately combining prior art; a motivation or suggestion to combine must exist." *Micro Chemical, Inc. v. Great Plains Chemical Co., Inc.*, 103 F.3d 1538, 41 USPQ2d 1238 (Fed. Cir. 1997).

It is submitted that it is only in hindsight that one can say that the disclosure of a GnRH antagonist having D-lysine modified by a reaction with naphthyl isocyanate would suggest that the now claimed peptides should be synthesized and would have a reasonable expectation of successfully exhibiting biopotency from the standpoint of long duration of action. It has previously been held that such a proposed combination of two references fails when there is no suggestion of such a combination, much less an indication that such a combination would have a reasonable expectation of success. Pertinent is the holding of the Court of Appeals of the Federal Circuit in the case of *In re Vaeck*, 20 USPQ 2d 1438, 1442 (Fed. Cir. 1991), where it was stated:

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary kill in the art that they should make the claimed composition or device, or carry out the claimed process; or (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*"

It is submitted that the single example of a GnRH antagonist having no substitution from the native molecule at the 5-position and D-Lys modified by reaction with naphthyl isocyanate at the 6-position does not fairly suggest that a similar compound having moieties in the 5-

and 6-positions which contain phenylalanine plus a carbamoyl or methylcarbamoyl modification would exhibit an extended duration of action in suppression of LH. It is thus submitted that amended claim 19 and new claim 22, which is dependent thereon, should be allowed.

In view of the foregoing amendments and remarks, it is believed that claims 1-11 and 13-22 are allowable, and allowance thereof is respectfully requested. It is believed that the application has accordingly been placed in condition for allowance, and favorable action is courteously solicited.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By: _____
James J. Schumann
Registration No. 20,856

February 2, 1998

Address all correspondence to:

FITCH, EVEN, TABIN & FLANNERY
135 So. LaSalle Street, Suite 900
Chicago, Illinois 60603
Telephone: (619) 552-1311